

REMARKS

The Applicants thank the Examiner for the examination to date and respectfully request reconsideration and allowance.

I. Status of the Claims

Claims 1, 7, 14, 17, 19, 21, 23-27, 34-40, 44, 46, 52, 55, 57, 59, 61-65, 71, 72, 80-85, 87-92, 94-99, 110-115, 117-129 are currently under examination. With this submission, no claims have been amended and no claims have been canceled. Hence, upon entry of this paper, claims 1, 7, 14, 17, 19, 21, 23-27, 34-40, 44, 46, 52, 55, 57, 59, 61-65, 71, 72, 80-85, 87-92, 94-99, 110-115, 117-129 will remain pending and under active consideration.

The independent claims are claims 1, 40, 90, 110-112, 120 and 123.

Applicants wish to thank the Examiner for reconsidering and withdrawing the 35 U.S.C. § 112, 2nd paragraph rejection.

One issue remains: obviousness.

II. 35 U.S.C. § 103 Rejections

The Examiner has rejected claim 1 and other independent claims (and dependent claims) as allegedly obvious in view of the combined teachings of WO 00/41214 (“Mirkin”) in view of US 2002/0098364 (“Bernard”) and US 2002/0063212 (“Mirkin 2002”). The Applicants respectfully traverse.

The Examiner states that Mirkin “fail[s] to teach that the adhesion layer is a hydrophilic compound that also inhibits protein adsorption.” (Office Action, page 3) Additionally, Examiner acknowledges that Mirkin does “not specifically teach patterning at a rate of 85 dots per 4 minutes.” (Office Action, page 3) However, Examiner argues that one of ordinary skill in the art would be motivated to combine Mirkin with Bernard, which teaches “stamps that have

been derivatized with polyethylene glycol,” (Office Action, page 3) to reduce protein absorption in order to transfer a high amount of compound to a substrate.

Applicants stress that the use of a modified tip yields unexpected results including a relatively fast printing speed which is reflected in the claims and was not achieved in the prior art. Additionally, the failure of others in the field to create a solution to the problem using a modified tip further demonstrates non-obviousness. Finally one of skill in the art would not combine Mirkin and Bernard to apply to protein patterning compounds.

A. Patterning Proteins can be Relatively Difficult

It was known at the time of the invention and continues to be known that patterning proteins and peptides (as opposed to generally smaller organic molecules) can be relatively difficult and/or slow. Specifically, for example, it was known in the art around the time period of around 1998-2000 that when proteins “contacted [an] AFM tip, they were known to stick to the tip, and would remain stuck during use of the tip in AFM.” (Reexam Control No. 90/007832 for Reexamination of US Patent No. 6,573,369; May 1, 2007 Rule 132 declaration by Dr. Curtis Mosher, paragraph 9; copy enclosed) Furthermore, Mosher points to Gergely et al. (*Proc. Nat. Acad. Sci. USA* 97: 10802-10807, 2000) stating “the protein has a higher affinity for the tip than for the surface.” (Gergely at 10804) Finally, Mosher found that “the proteins remained associated with the AFM tip, and we were unable to transfer any protein in sub-micron domains from the tip to the substrate.” (Mosher declaration paragraph 10). Hence, patterning proteins at fast printing speed, as presently claimed, was not an easy undertaking.

In fact, as stated in a paper by some of the present inventors, Lim et al. (*Angew. Chem Int. Ed.* 42: 2309-2312, 2003) “methods must be developed for facilitating the transport of the high-molecular-weight biomolecules from a coated tip to a substrate without sacrificing sub-100-nm resolution and patterning speed.” At the time of filing, indirect methods were preferably used to pattern proteins. Furthermore, Lim states “in the absence of this tip coating, the protein inking

solutions...do not wet the silicon nitride cantilevers. We have found that untreated cantilevers often produce inconsistent or low-density protein patterns.” (Lim at page 2310, line 48-52).

Additionally, Lim affirms that researchers had to develop special approaches to direct patterning of proteins by DPN. Specifically, these approaches include: (1) the use of a chemically tailored form of collagen that has a surface-binding group built into it to help facilitate nanostructure absorption, and (2) the use of glass pretreated with 3-glycidooxypropyltrimethoxysilane. The first approach alters the protein that is used. The second approach alters the surface that is used. Another approach, including the approached noted in the Mosher declaration, was to modify the protein ink solution. In contrast, inventors have developed an unique approach to the problem that does not modify either the substrate or the surface, or the ink solution, but rather modifies the tip. This approach developed by the inventors is advantageous because it leaves the substrate, protein, and ink in a more natural state than the alternative approaches.

Additional workers in the field have published articles supporting the difficulty of patterning proteins and peptides. For example, Jung et al. also noted that “[d]irect patterning of biological materials such as DNA, peptides, and proteins at the nanoscale without loss of activity requires the ability to immobilize these biomolecules through specific recognition chemistries that minimize nonspecific binding.” (Jung et al., *Nano Letters* 4:2171 (2004))

In their Working Example 1, applicants also confirm the difficulty in patterning proteins. Specifically, applicants state “[i]n the absence of this tip coating, the protein inking solutions...may not in some cases wet the untreated silicon nitride cantilevers. Hence, untreated cantilevers can result in some cases in inconsistent, or low-density protein patterns.” (Specification, page 22)

Hence, a need existed for the presently claimed inventions and the applicants unexpectedly found an effective method to address this need, experimentally demonstrating the invention. Direct printing of proteins – in contrast to mere absorbing proteins onto pre-patterned

surfaces - allows better use of multiple proteins rather than a method wherein a single type of protein is adsorbed to a patterned surface. Moreover, the direct approach better facilitates retention of natural biological activity as the protein does not need to be modified.

B. Neither Mirkin, Bernard, nor Mirkin 2002 Alone or in Combination Teach the Claimed Invention

As correctly recognized by the Examiner, Mirkin fails to teach **inhibition** of protein adsorption on a tip coated with an adhesion layer. Instead, Mirkin focuses on tip modification to **improve adherence** to the tip via an adhesion layer. In contrast, the claimed invention teaches a method to **reduce adherence** of proteins to the tip. Thus, Mirkin actually teaches away from the claimed invention. Mirkin teaches cleaning which may be a useful step but is not sufficient to generate the presently claimed protein printing speeds.

Bernard does not provide the missing teachings required by the Office's rejection. Bernard is focused on a stamping process which is not focused on protein printing, but highly polar inks. Thus, Bernard describes and suggests nothing with respect to protein printing.

Additionally, the stamping techniques described in Bernard are inherently different from the tips used in the claimed inventions. Specifically, the patterning compound moves down the tip and onto the substrate and thus away from the tip (like an ink pen). In contrast, the patterning compound in a stamp does not move down the stamp as with a tip. Thus, there would be no motivation to combine Bernard with Mirkin.

Finally, Mirkin 2002 also does not provide the missing teachings required by the Office's rejection. Specifically, Mirkin 2002 does not teach that proteins can be efficiently patterned using a tip modified to resist protein adsorption.

In sum, there is no *prima facie* obviousness present in the record. Even the combination of Mirkin, Bernard, Mirkin 2002, and Duffy would not lead to the current claims as other methodologies are provided in these articles for the person of skill in the art which do not generate the claimed printing speeds. Additionally, one skilled in the art would not be motivated

to turn to Mirkin or Bernard or to their combined teachings, to arrive at the claimed invention. Thus, the current claims are not rendered obvious by the cited prior art.

Moreover, the applicants workings examples rebut any prima facie obviousness. Specifically, working example 1 describes the use of a modified AFM tip that inhibits protein adsorption and thus facilitates protein transport from the tip to the surface. Success of this model was verified by patterning of anti- rabbit IgG and and rabbit IgG. (Specification page 24) Furthermore, conformation of success was verified by fluorescence microscopy. (Specification page 24).

In a telephone interview dated March 20, 2009, the Examiner suggested that unexpected results could be useful in demonstrating the advantages. However, the applicants respectfully submit that the filed application comprises unexpected results sufficient to rebut prima facie obviousness. The prior art Mirkin teachings cannot provide the speed of printing presently claimed for proteins and peptide.

Finally, claim 97 and the Duffy reference are not discussed in this response because dependent claim 97 is allowable based on the above arguments.

CONCLUSIONS

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even

entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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